REMARKS

Claims 20, 49, 51, 56, 57, 59 and 65-67 previously were pending in the subject application. By this amendment, Applicants have amended without prejudice claims 49, 51, 57, 59, 66, and 67, canceled without prejudice claim 56, and introduced new dependent claim 68. The amendments and new claims are fully supported at least by paragraphs 0005, 0011, 0012, 0013, 0015, 0030, 0081-0091, 0176-0180, and 0196 of the published application in view of the knowledge of the person of ordinary skill in the art. Applicants maintain that the claim amendments and new claims do not introduce new matter. Accordingly, Applicants respectfully request that the Examiner enter this Amendment. Upon entry of this Amendment, claims 20, 49, 51, 57, 59 and 65-68 will be pending and under examination.

I. Status of Case

A. Rejections Withdrawn in Part

In view of Applicants' previous amendment and accompanying declaration by Dr. Rosen, the Examiner acknowledges that the specification enables a method of expressing a functional HCN2 ion channel in the mammalian heart, a method of inducing a pacemaker current in a mammal's heart, and a method of inducing pacemaker current in a cardiomyocyte. *See* Office Action at 3-5 (July 24, 2008). The Examiner also acknowledges that introduction of the composition of Claim 20 by injection, microinjection, and catheterization are enabled, in view of Applicants' previous amendment and the accompanying declaration of Dr. Rosen. *See id.* at 4. The Examiner thus has withdrawn the rejection of claims 49, 57, 59, 66, and 67 to the extent that they "read on a method of expressing functional HCN2 ion channel in a mammalian heart by directly injecting the composition by injection, microinjection or cardiac catheterization." *Id.* at 4.

The Examiner has maintained the rejection of method 49, directed to a method of expressing a functional HCN2 ion channel in a mammalian heart, and of method claims 57, 59, 66, and 67, directed to a method of inducing a pacemaker current, on enablement grounds to the extent that these claims encompass "topical administration." As discussed below, in order to

obviate the Examiner's enablement rejections and to expedite prosecution, Applicants have amended the claims to specifically recite that the composition is administered "by injection, microinjection, or catheterization." Thus, reference to topical administration has been deleted from these method claims. Applicants maintain that these method claims as pending prior to this amendment were allowable. These amendments have been made to expedite allowance of the claimed subject matter and without prejudice to our right to pursue the prior claims in subsequent prosecution. We submit that these claims as now presented are enabled and should be allowed.

Also, the Examiner has maintained the rejection of method of treating claims 51 and 56 on enablement grounds to the extent that they encompass "topical administration" and because the specification allegedly does not enable a method of treating. As discussed below, in order to obviate the Examiner's enablement rejections, claim 56 has been cancelled and claim 51 has been amended to specifically recite that the composition is administered "by injection, microinjection, or catheterization." Thus, reference to topical administration has been deleted from these method claims. Also, the claims have been amended to recite that the composition comprises human cells and is administered to a "human." Applicants maintain that these method claims as pending prior to this amendment were allowable. These amendments have been made to expedite allowance of the claimed subject matter and without prejudice to our right to pursue the prior claims in subsequent prosecution. We submit that these claims as now presented are enabled and should be allowed.

Further, in view of Applicants' prior response, the previous rejection of claims 20, 49, 57, and 65-67 for obviousness has been withdrawn. A new rejection of composition claims 20 and 65 has been set forth. For reasons discussed below, Applicants believe that this rejection should be withdrawn and the composition claims allowed. New composition claim 68, depending from claim 65, has been added, reciting that the mesenchymal stem cell is "human."

The Examiner has also withdrawn the rejection of claims 20 and 65 for indefiniteness in view of Applicants' prior response.

II. Response to Rejections

A. Rejection of claims 49, 51, 56, 57, 59, 66, 67 under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 49, 51, 56, 57, 59, 66, 67 stand rejected as not enabled. According to the current rejection, the specification does not enable a method of treating any cardiac rhythm disorder and does not enable topical administration to cells of the heart for treating, expressing, or inducing current in the heart. *See id.* at 4, 11-12.

1. Topical Application

Applicants maintain that topical application is enabled by the specification at least for the reasons set forth in the previous amendment. Applicants note, however, that this rejection does not apply to the claims now pending. The rejection on this basis therefore should be withdrawn.

Accordingly, those claims directed to methods of "inducing a pacemaker current" or "expressing a functional hyperpolarization activated, cyclic nucleotide gated 2 (HCN2) ion channel" (i.e., claims 49, 57, 59, 66, and 67) as presented by this amendment should be allowed. For reasons discussed below, Applicants also submit that the amended claim directed to a method of treating should also be allowed.

2. Treating

a. Cell Differentiation and Host Rejection

The Examiner's bases for finding treating not enabled appear to fall into two categories. The **first** category includes the Examiner's allegations that there are uncertainties about transplanting mesenchymal stem cells ("MSCs") into a recipient's heart, including the potential for host rejection of foreign MSCs and the possible differentiation of the MSCs in the heart into unwanted cell lineages. *See id.* at 5-7.

That part of the claim rejection that alleges that the host will reject foreign MSCs appears to be confined to xenogenic transplantation, and not to include allogeneic transplantation. *See* Office Action at 7-8, 11. The claims to method of treating have been amended without prejudice to encompass only transplantation of "human" cells into a "human" heart. This ground for

rejection therefore no longer applies. This conclusion is supported by a recently-reported clinical trial in which no rejection of human MSCs transplanted into humans was observed at the six-month follow-up date. *See* Joshua Hare et al., *A randomized, double-blind, placebo-controlled, dose-escalation study of intravenous adult human mesenchymal stem cells (Prochymal™) following acute myocardial infarction*, American College of Cardiology conference (poster presentation) at 4 (2007) (finding "[n]o increase [relative to placebo] in ectopic tissue formation or events suggesting immunologic reactions") (emphasis added) (attached as Exhibit A).

Regarding alleged possible differentiation of hMSCs into other unwanted cell types when transplanted into human cardiac tissue, the Examiner seems primarily concerned that the stem cells will differentiate into a cell type not normally present in the heart ("unwanted cell lineages"), such as bone or cartilage, even when site-specifically introduced, as per the pending claims. *See* Office Action at 5-6. This objection is not substantiated by any actual observed differentiation. That is, the references cited in the Office Action provide no data indicating that differentiation of MSCs was actually observed, and, in particular, they provide no data indicating that MSCs differentiate into cell types not normally present in the heart, particularly when site-specifically administered. In fact, in the clinical trial mentioned above, no adverse effects were observed that were attributable to stem cell transplantation. Thus, if differentiation did occur, it did not produce a detected adverse effect (such as, for example, loss of the hMSCs' immunoprivileged status).[1] *See* Hare et al. at 2 (data indicating no significant difference in occurrence of adverse events between MSC recipients and placebo recipients), 4 ("IV administration of allogeneic MSCs is safe and well tolerated at all dose levels," and referring to the "excellent safety profile of allogeneic MSCs"). This supports Applicants' position that the Examiners' objections on safety and/or side effects grounds (*see, e.g.*, Office Action at 5-9) relating to, *inter alia*, differentiation, are unfounded at least in the context of the amended claims.

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[1] The Examiner raises the possibility of exacerbation of atherosclerosis, arrhythmogenesis, inappropriate calcification and local or ectopic tumor formation, but provides no supporting data. *See* Office Action at 8, 11. Applicants contend that, in the absence of such data, the rejection should be withdrawn. Applicants note hat the MSC transplantation clinical study cited above found no adverse effects attributable to the transplanted MSCs at the six-month follow-up, suggesting that the alleged potential side effects are illusory, particularly in the context of the amended claims. *See* Hare at 2, 4. If anything, the cited references indicate that MSCs as in Applicants' invention would not present a risk of arrhythmia. *See, e.g.*, Mocini et al., Ital. Heart J. 6: 267, 267 (2005) (of record), Abstract ("As a matter of fact, the use…of stem cells from bone marrow has not been associated with any significant cardiac rhythm disturbance." (emphasis added)) This basis for rejection should therefore be withdrawn.

Further, as noted in the previous amendment, the claimed methods do not purport to provide a permanent cure of the treated condition. Treating as claimed is useful under 35 U.S.C. § 101 because it at least mitigates the detrimental effects of the treated condition, even if it does not provide a permanent, lifelong cure with no possibility of side effects or failure.

b. Different Etiology of Conditions to be Treated

The Examiner's **second** basis for finding treatment not enabled is that "it is not clear that" delivery of the MSCs as recited in the claims can treat all cardiac rhythm disorders because different cardiac rhythm disorders have "different etiology and pathology." *See* Office Action at 9-11. To the contrary, the claimed method of treating is applied to cardiac rhythm disorders that share a common deficit, aberrant pacemaker function, and the supplying of MSCs expressing HCN2 provides the ability to generate pacemaker current, regardless of the etiology or pathology of the disorder, because the recipient hearts all have in common other qualities that make them susceptible to such treatment. These qualities include being comprised of cardiac myocytes that share, among other things, the ability to establish junctions with other cells and the ability to respond to an electrical impulse by propagating that impulse in a regular fashion. In view of these common features, the disparate etiologies set forth at length are not material to the claimed methods' efficacy. *See* Office Action at 9-11.

A declaration by Dr. Rosen was submitted with the last Amendment. Among other things, the declaration indicates that the ordinarily skilled artisan, guided by the instant specification, would have been able to treat conduction block, complete atrioventricular block, incomplete atrioventricular block or sinus node dysfunction by contacting the cells of the heart with hMSCs incorporated with HCN2. *See* Declaration by Dr. Rosen ¶ 10 (May 1, 2007). This is because the dog model is representative of a variety of rhythm disorders.

The Plotnikov reference (Circulation 116: 706 (2007), cited above and in the Office Action and previous amendment) demonstrates a therapeutic effect, *i.e.* treatment, by demonstrating that administration of hMSCs incorporated with mHCN2 to dogs in complete heart block (the method disclosed in the instant specification) yielded catecholamine-responsive, regular-rhythm pacemaker function at a rate of greater than 50 beats per minute. *See* Plotnikov at

706, 708-709.[2] More specifically, in Plotnikov, complete heart block in dogs was induced via radiofrequency ablation of the atrioventricular node. *See* Plotnikov at 707. Human MSCs incorporated with murine HCN2 were then injected into the left ventricular anterior wall. *See id.* The person of ordinary skill in the art would have recognized that the result, the production of a regular rhythm of greater than fifty beats per minute, *see id.* at 708-09 and Figure 3, constitutes a therapeutic effect. This is the desired beat rate with electronic pacemakers in humans. *See id.* at 712 ("We believe that an ideal biological pacemaker would have minimal rates in the 50s and be capable of achieving rates of 100 to 150 bpm under catecholamine demand.").

Thus, contrary to the Examiner's reasoning, the person of ordinary skill in the art would not have had to "empirically perform the method in different animal model to test of claimed composition could treat conditions embraced by the breadth of instant claims," Office Action at 11. The person of ordinary skill in the art would have been able to determine appropriate dosage and to use the claimed method to treat the disorders within the scope of the method of treatment claims without undue experimentation.

Accordingly, for all the foregoing reasons, particularly in light of Dr. Rosen's previously submitted declaration, the person of ordinary skill in the art could implement the claimed method of treating without undue experimentation. Applicants therefore respectfully request that the rejection based on lack of enablement of treating be withdrawn.

II. Rejection of Claims 20 and 65 as Obvious

Applicants note that the previous rejection of claims 20, 49, 57, and 65-67 was withdrawn in view of Applicants' argument. The Examiner has set forth a new basis for rejecting composition claims 20 and 65 as obvious over the prior art references Pittenger (U.S. Patent No.

[2] Plotnikov demonstrates that those skilled in the art could have madeand used the invention without undue experimentation. For example, experiments show that appropriate efficacious dosages can readily be determined. The person of ordinary skill in the art could have readily determined the appropriate concentration of MSC cells that would be effective in the treatment of a particular cardiac disorder or condition. Such concentrations will depend on the nature of the disorder or condition, and could have been determined by standard clinical techniques. The precise dose of MSCs to be employed in the method of treatment will also depend on the route of administration, and the seriousness of the disease or disorder, and can be decided according to the judgment of the practitioner and each patient's circumstances. Thus, Plotnikov may be properly cited to demonstrate that the disclosures in the specification as filed are sufficient to enable a person skilled in the art to practice the invention being claimed

6,387,369), Jansen (U.S. Patent No. 6,979,532), and Wang (J. Thorac. Cardiovasc. Surg. 120: 999 (2000)).

A. Pittenger (United States Patent No. 6,387,369)

According to the Examiner, Pittenger teaches genetically modifying MSCs to express varieties ("verities") of genes of interest, using viral or non-viral vectors. *See* Office Action at 13. The Examiner concedes that Pittenger differs from the claimed invention "by not explicitly teaching transfecting cells with nucleic acid encoding HCN2." *Id.* at 13. However, the Examiner fails to recognize that Pittenger also differs from the claimed invention because Pittenger is concerned with regeneration and repair, not with providing a pacemaker current. Pittenger's distinct purpose thus leads away from combining with Jansen and Wang.

To elaborate, Pittenger is concerned with using MSCs to regenerate or repair striated cardiac muscle, as the Examiner acknowledges. *See* Office Action at 13, Pittenger at col. 1, ll. 42-45. Pittenger is further concerned with genetically engineering the MSCs so that they express proteins of importance for differentiation and/or maintenance of striated muscle cells, such as growth factors, transcription factors, cytokines. *See* Pittenger at col. 2, ll. 51-65. Pittenger is properly understood to purport to disclose a means for regeneration and repair of cardiac tissue by implanting cells that secrete factors (produced as a consequence of the genetic engineering of the MSCs) that will promote the differentiation of the implanted cells into cardiomyocytes and the subsequent maintenance of the new cardiomyocytes, thereby compensating for the loss of tissue due to injury and/or disease. *See* Pittenger at col. 1, ll. 41-59, col. 2, ll. 43-47, and col. 4, ll. 8-15.[3]

Pittenger does not provide an electrical pacing mechanism provided by a transgene incorporated into MSCs, as in the present invention. Pittenger has a completely different purpose from the claimed inventions. Also, unlike Jansen (discussed in further detail below), Pittenger is not concerned with identifying substances that modulate the activity of membrane channels or

without undue experimentation, *i.e.*, to demonstrate that the disclosure was enabling as of the filing date.

[3] Applicants note, however, that Pittenger provides no evidence that the transfected cells (let alone cells transfected with other genes, such as Applicants' HCN2) actually differentiate. The Examples in Pittenger are written in the present tense with respect to the presence of detectable surface markers that indicate differentiation;

any other protein.

B. Jansen

According to the Examiner, Jansen cures Pittenger's deficiency by disclosing the provision of mammalian cells that express a hyperpolarization-activated cation channel including HCN2 and determining the membrane potential of the cells. *See* Office Action at 14. According to the Examiner, Jansen further teaches a method for identifying substances that modulate the activity of hyperpolarization-activated cation channels using genetically modified mammalian host cells that express HCN2, but does "not explicitly teach a [sic] transfecting HCN2 in MSC." *See id.* at 14.

To elaborate, Jansen teaches an in vitro fluorescent screening assay that can be used to identify substances that modulate the activity of hyperpolarization-activated cation channels. *See* Jansen at col. 2, ll. 7-31. The mouse HCN2 gene was used to transform HEK and CHO cells. Jansen also teaches the use of wild-type HCN2. Jansen does not disclose or refer to the use of MSCs, either explicitly or implicitly.

C. Wang

According to the Examiner, Wang teaches "administration of MSC in the heart shows growth potential in a myocardial environment and indicated the formation of gap junctions (see abstract and Figure 6). However, Wang et al do not teach composition comprising MSC compromising [sic, comprising] HCN2."

To elaborate, Wang teaches the administration of MSCs to a heart to mitigate or reverse the loss of heart cells that results from heart failure (via, e.g., necrosis or apoptosis). *See* Wang at 999, 1003-04. The cells used in Wang are not incorporated with any DNA (let alone DNA that encodes HCN2) and the condition treated in Wang is cardiac cell loss, not cardiac arrhythmia.

D. References in Combination

As acknowledged by the Examiner, Pittenger does not teach the delivery of a pacemaker

Pittenger provides no evidence that such markers were present or detected.

current. Pittenger is concerned with repair, not pacemaker current. Accordingly, it would be contrary to Pittenger's goals to replace the repair/differentiation genes with a pacemaker ion channel such as HCN2. Hence, Pittenger leads away from the Examiner's proposed combination of Pittenger with Jansen.

According to the Examiner, it would have been obvious to modify the composition of Pittenger "with Jansen" by substituting HCN2 for the genes that Pittenger used to transform MSCs. *See* Office Action at 14. According to the Examiner, motivation to use HCN2 derives from the fact that "Jansen had already shown that HCN2 could be expressed in mammalian cells to determine membrane potential....[G]iven that MSC were available for use to express gene of interest as per the teachings of Pittenger it would have [been] obvious for one of ordinary skill in the art to use HCN isoform including HCN2 to produce transformed cells as disclosed in the instant application." *Id.* at 14. The Examiner further asserts that the person of ordinary skill in the art would have had a reasonable expectation of success in practicing the claimed composition because "the art had already shown that HCN2 and other ion channel isoform could be expressed in mammalian cell." *Id.* at 14-15. Further, "it was routine in the art at the time of filing to genetically modify mesenchymal stem cells by substituting the coding sequence of one transgenes with an other gene of interest."

Again, however, Pittenger leads away from the modification that the Examiner proposes. It would be contrary to the teachings of Pittenger to substitute Pittenger's genes with the gene disclosed by Jansen. As indicated, Pittenger is concerned with transfecting cells with genes pertinent to cardiac tissue repair or differentiation. It would be contrary to Pittenger's teaching to make the modification proposed by the Examiner because such a modification (use of an ion channel such as HCN2) would not provide the repair/differentiation function that Pittenger is trying to achieve. Nor would Pittenger's teaching have been furthered by substituting a nucleic acid encoding HCN2 for the growth factors, myogenic factors, transcription factors, cytokines, neuregulins, homeobox genes, or genes encoding factors that stimulate angiogenesis or revascularization that Pittenger proposes to use (*see* Pittenger at col. 2, ll. 51-62) because HCN2 does not provide a function like that of the listed factors which, as noted above, are supposed to promote MSC differentiation and to promote maintenance of the differentiated cells. HCN2 does

not function to promote differentiation or maintenance of differentiated cells.

Nor does Jansen point toward the claimed composition. Jansen is concerned with an in vitro assay for identifying molecules that modulate HCN channels. *See* Jansen at col. 1, ll. 14-17 and ll. 51-55 (summarizing the invention as a process that permits high-throughput screening for modulators of an HCN channel). Thus, Jansen is concerned with identifying modulators of HCNs, presumable in order to use those modulators to alter HCN activity in some other context. Jansen is not concerned with the use of HCN to perform some function in a cell in vivo. Certainly there is no motivation to transfect Pittenger's stem cells with an HCN channel-and as discussed above, that would be contrary to Pittenger's teaching.

Nor do Jansen and Pittenger suggest that they should be combined with each other, since they concern completely distinct goals-in vivo cardiac repair and regeneration (Pittenger) and in vitro identification of HCN modulators. Nor has the Examiner identified any reason (such as "a known problem for which there was an obvious solution encompassed by the patent's claims," *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1742 (2007)) for the person of ordinary skill in the art to combine Jansen's in vitro use of HCNs with Pittenger's in vivo use of completely distinct genes to prepare the claimed composition.

Since Wang does not concern the use of HCN2, it also, either alone or in combination with Pittenger and Jansen, does not suggest the claimed composition.

Applicants further respectfully disagree with the Examiner's analysis because, contrary to the Examiner's reasoning, the cited alleged disclosures provide no motivation to modify Pittenger. "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). The Examiner states that the mere availability of a technique for expressing HCN2 in mammalian cells would provide motivation. Applicants contend that this does not amount to motivation because the Examiner has identified nothing that would motivate the person of ordinary skill in the art to combine Jansen with Pittenger. The mere existence of Jansen does not amount to motivation. Pittenger is concerned with the use of transgenes important for "differentiation and/or maintenance" (Pittenger at col. 2, ll. 51-54).

HCN2 is important for electrical conduction, not differentiation or maintenance. The person of ordinary skill in the art therefore would not have been motivated by the mere fact that cells had been transfected with an HCN2 gene to combine that with Pittenger's use of MSCs for differentiation and/or maintenance. It is clear that the Examiner has impermissibly used hindsight and the Applicants' application as a blueprint to identify and combine Pittenger Jansen. "A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." *KSR*, 127 S. Ct. at 1742 It can only be concluded that no case for *prima facie* obviousness of the claimed compositions can be based on the cited Pittenger and Jansen references.

This is not a case where "there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions." *KSR*, 127 S. Ct. at 1742. Rather, there was a vast number of different genes that could be substituted for those that Pittenger used. Nor was the "prior art [ ] replete with" indications that Pittenger's method should be modified. *See id.* This is not a case where "ordinary skill and common sense" yield a modification of the cited prior art that results in the claimed compositions. Rather, this is a case where a novel, non-obvious composition has been invented for use in what the Examiner concedes is a novel, non-obvious method. There would thus be no reason to combine Pittenger with Jansen as the Examiner proposes (and, for reasons set forth above, it would be contrary to Pittenger's teaching to substitute the genes used by Jansen for the genes used by Pittenger).

Wang does not provide the missing motivation. According to the Examiner, Wang relates to administration of MSCs to the heart. *See* Office Action at 14. The Examiner points to nothing in Wang that relates to what gene should be incorporated into the MSCs that are administered to the heart.

For the foregoing reasons, Pittenger leads away from the combination proposed by the Examiner. Applicants therefore respectfully request that the Examiner withdraw the rejection of claims 20 and 65 as obvious.

VI. Double Patenting Rejections

The Examiner has provisionally rejected claims 20, 49, 51, 56-57, 59, 65-67 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1, 4, 12, 39, and 65-75 of co-pending Application No. 10/342,506 ("the '506 application"), which corresponds to U.S. Publication No. 20040137621.

Applicants note that this is a "provisional" rejection over the '506 application which is not an allowed application. Accordingly, if the now pending claims of the subject application are otherwise allowable, the present provisional double patenting rejections should be withdrawn and the claims in the subject application should be allowed and issued, whereby the claims of the '506 application would become subject to an obviousness-type double patenting rejection. At that time, applicant will consider filing a terminal disclaimer, if necessary.

CONCLUSION

In view of the remarks made hereinabove, Applicants respectfully request that the Examiner reconsider and withdraw the rejections set forth in the July 24, 2008 Non-Final Office Action, and earnestly solicit allowance of the now pending claims.

If a telephone interview would assist in expediting prosecution of the subject application, the Examiner is invited to telephone the undersigned at the number provided below. No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 11-0600.

Respectfully submitted,

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Date: Jan. 26, 2009

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